REMARKS

Applicants have canceled claims 30-31 and 59-62 without prejudice. Claims 26, 34, 63, and 64 have been amended solely for greater clarity. Support for the amendments can be found throughout the specification. No new matter has been introduced.

Applicants note with appreciation that the Examiner has withdrawn claim rejections under 35 U.S.C. § 102(b) and § 101.

Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action.

Double patenting

Claims 26-34 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-23 of copending Application No. 10/949,720.

Applicants respectfully request the Examiner hold this rejection in abeyance until allowable subject matter is found; at which point, Applicants will submit a terminal disclaimer if deemed necessary.

Applicants further point out that "[i]f a provisional double patenting rejection (of any type) is the only rejection remaining in two conflicting applications, the examiner should withdraw that rejection in one of the applications (e.g., the application with the earlier filing date) and permit the application to issue as a patent. The examiner should maintain the provisional double patenting rejection in the other application which rejection will be converted into a double patenting rejection when the first application issues as a patent." See M.P.E.P. § 1504.06.

Rejections of Claims 63-64 under 35 U.S.C. § 101

The Examiner alleges that claims 63 and 64 are directed to non-statutory subject matter. Applicants have amended claim 63 to recite "an isolated" as suggested by the Examiner. Claim 64 has been amended to recite "non-human" transgenic animals to comply with 35 U.S.C. § 101. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

Rejections of Claims 26-29, 31-34, and 63-68 under 35 U.S.C. § 103(a)

Claims 26-29, 31-34, and 63-68 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Stephenson et al. (BMC Molecular Biology, 12/21/2001, 2(15):1-9) in view of Queen et al. (US Patent No. 5,693,762). Specifically, the Examiner alleges that Stephenson et al disclose that EphB4 is over-expressed in colon cancer and that "therapies targeting EphB4 protein could be used in anticancer treatments." Relying on these teachings the Examiner argues that one of ordinary skill in the art would have been motivated to create radioisotope, fluorescent, enzyme, and enzyme co-factor labeled antibodies (e.g., bispecific, chimeric, human and humanized antibodies) because these antibodies would function as diagnostic and therapeutic agents that recruit effector molecules (toxins, drugs, prodrugs, cytokines, radionucleotides) or effector cells (cytotoxic T lymphocytes, NK cells, macrophages, granulocytes) to the colon cancer cells expressing EphB4. Applicants respectfully traverse this rejection.

Pursuant to MPEP 2143, "[t]o establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the reference themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations."

First, the cited references fail to provide any motivation leading the skilled artisan to combine the teaching of Stephenson et al. and Queen et al. Stephenson et al. disclose a polyclonal EphB4 antibody (H-200) which was raised against an extracellular domain of an EphB4 protein. However, this antibody was used merely for detecting expression levels of the EphB4 protein to determine whether EphB4 is overexpressed in colon cancer cells. Stephenson et al. speculate that because EphB4 is over expressed in colon cancer cells that the "Eph-ephrin signalling may be important in the progression of colon cancer and that therapies that target this receptor may find application in anti-cancer systems." (emphasis added.)

Stephenson et al. do not teach that inhibition of EphB4 would promote apoptosis in colon cancer cells. They do not suggest that one could use inhibitors of either Eph receptors or Ephrin as anti-cancer therapeutics. No *in vitro* inhibition data, no *in vivo* inhibition data, and no animal models demonstrating such benefits have been taught. In fact, no inhibitors have been disclosed. Moreover, Stephenson et al. admit that the role of EphB4 and other Eph receptor family members in cancer has not yet been defined."

Preliminarily, Applicants believe that based on the teachings of Stephenson et al. the skilled artisan would not be motivated to make even monoclonal antibodies against EphB4. Stephenson et al. provide no motivation to do so. Although Queen et al. disclose methods for producing humanized immunoglobulins, antibody fragments, bifunctional antibodies, and single chain antibodies, one of skill in the art would not have been motivated to modify the polyclonal antibodies disclosed by Stephenson et al. using the methods taught by Queen et al. Because the skilled artisan would have no reason to believe that the polyclonal antibodies of Stephenson et al. could inhibit the Eph-Ephrin signalling pathway or promote apoptosis. Absent any teachings in Stephenson et al. that the EphB4 polyclonal antibody may have any therapeutic value, one of ordinary of skill would not have been motivated to modify Stephenson's antibody to make bispecific, single-chain, chimeric, human, and humanized antibodies against EphB4 as claimed in the present invention.

Second, the cited references fail to provide a reasonable expectation of success that antibodies to EphB4 would be effective in promoting apoptosis. The Examiner asserts that "one of skill in the art would recognize that the antibodies taught by the combined teachings of Stephenson et al and Queen et al would inhibit activities of EphB4. Absent a showing otherwise, the antibodies taught by the combined teachings of Stephenson et al and Queen et al would inhibit the interaction between Ephrin B2 and EphB4, inhibit clustering of EphB4, inhibit angiogenesis, and promote tumor regression." See Office Action, page 10, lines 7-16. Applicants respectfully disagree.

To establish a prima facie case of obviousness against the claimed invention, the Examiner has to show that a skilled artisan would have predicted with a reasonable expectation of success which specific EphB4 antibody is effective in promoting apoptosis in a tumor cell. The following

statement, quoted from a decision by the Board upholding claims to monoclonal antibodies, is believed to be particularly relevant to the issue at hand: "Hybridoma technology is an empirical art in which the routineer is unable to foresee **what particular antibodies** will be produced and which specific surface antigens will be recognized by them (emphasis added)." Ex parte Old, 299 U.S.P.Q. 196, 200 (PTO Bd. App. 1985). In view of the unpredictability of the antibody art, one skilled in the art could not have foreseen with a reasonable expectation of success in making the presently claimed antibody.

Lastly, the cited references when combined do not teach all the claim limitations. Independent claim 26 as amended is directed to an isolated antibody which binds to an extracellular domain of an EphB4 protein and promotes apoptosis in a tumor cell, wherein the antibody is selected from bispecific, single-chain, chimeric, human, and humanized antibodies. The combination of Stephenson et al. and Queen et al. fail to provide the claimed antibody. Accordingly, the combination of Stephenson et al. and Queen et al. still fails to teach all the claim limitations.

Additionally, the Examiner contends:

> ". . . one of skill in the art would recognize that the antibodies taught by the combined teachings of Stephenson et al. and Queen et al. would inhibit activities of EphB4. Absent a showing otherwise, the antibodies taught by the combined teachings of Stephenson et al. and Queen et al. would inhibit the interaction between Ephrin B2 and EphB4, inhibit clustering of EphB4, inhibit angiogenesis, and promote tumor regression. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the antibodies of the prior art do not possess the same characteristics as the claimed antibodies. In the absence of evidence to the contrary, the burden is on Applicant to prove that the claimed antibodies are different from those taught by the prior art and to establish patentable differences." See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2nd 1992 (PTO Bd. Pat. App. & Int. 1989).

In sum, it appears that the Examiner believes that the antibody as taught by the combination of Stephenson et al. and Queen et al. would necessarily possess the claimed characteristics.

Applicants respectfully submit that inherent characteristics cannot be obvious to one of ordinary skill in the art. MPEP 2112 clearly points out that "[T]he fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic." Further, one court observed that "a retrospective view of inherency is not a substitute for some teaching or suggestion supporting an obviousness rejection." *In re* Rijckaert, 9 F.3d 1531, 1534 (Fed. Cir. 1993). Accordingly, the proposed combination of the cited references fails to teach each and every limitation of the claimed invention.

In sum, Applicants submit that all of the pending claims are non-obvious over Stephenson et al. in view of Queen et al. Applicants respectfully request reconsideration and withdrawal of the rejection of the pending claims under 35 USC § 103.

Rejections of Claims 26-34 and 63-68 under 35 U.S.C. § 103(a)

Claims 26-34 and 63-68 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Inada et al. (Blood, 1997, 89(8):2757-2765) in view of Queen et al. (US Patent No. 5,693,762). Applicants respectfully traverse these rejections.

Like Stephenson et al., Inada et al. disclose use of EphB4 antibodies merely for **detecting** expression levels of the EphB4 protein. Inada et al. do not suggest or teach any therapeutic use or potential of the EphB4 antibody. Absent any teachings in Inada et al. that the EphB4 antibody may have any therapeutic value, one of ordinary of skill would not have been motivated to modify Inada's antibodies to make bispecific, single-chain, chimeric, human, and humanized antibodies against EphB4 as claimed in the present invention.

Similarly, the Examiner has failed to show that a skilled artisan would have predicted with a reasonable expectation of success that an EphB4 antibody is capable of promoting apoptosis in a tumor cell.

Like Stephenson et al, Inada et al. do not suggest or teach an isolated EphB4 antibody which promotes apoptosis in a tumor cell. Inada et al. merely use antibodies to EphB4 to isolate arythroid progenitor cells. No diagnostic or therapeutic benefits of these antibodies have been disclosed.

Queen et al., fail to overcome the deficiencies of Inada et al. Therefore, the proposed combination of the cited references fails to teach each and every limitation of the claimed invention.

In sum, Applicants submit that all of the pending claims are non-obvious over Inada et al. in view of Queen et al. Applicants respectfully request reconsideration and withdrawal of the rejection of the pending claims under 35 USC § 103.

Rejections of Claim 26 under 35 U.S.C. § 112, First Paragraph

Claim 26 and its dependent claims are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. The Examiner asserts that this is a new matter rejection. Applicants respectfully disagree.

Specifically, the Examiner asserts that "[d]escriptions of 'human' and 'syngeneic' antibodies that specifically bind the extracellular domain of an EphB4 protein are not found in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the invention was filed, had possession of the claimed invention." Office Action, page 14, lines 13-18.

Applicants submit that the recitation of "syngeneic" antibodies is fully supported by the original specification. For example, the specification describes that "[i]t is understood that antibodies of the invention may be polyclonal or monoclonal; intact or truncated, e.g., F(ab')2, Fab, Fv; xenogeneic, allogeneic, **syngeneic**, or modified forms thereof, e.g., humanized, chimeric, etc." (see, e.g., page 30, line 29; page 31, lines 1-2, emphasis added).

Applicants further submit that the recitation of "human" antibodies is fully supported by the original specification. For example,, the specification teaches that "[s]uch techniques are well known in the art, and include, for example, the hybridoma technique (originally developed by Kohler and Milstein, (1975) Nature, 256: 495-497), the **human** B cell hybridoma technique (Kozbar et al., (1983) Immunology Today, 4: 72), and the EBV-hybridoma technique to produce **human** monoclonal antibodies (Cole et al., (1985) Monoclonal Antibodies and Cancer Therapy, Alan R. Liss, Inc. pp. 77-96) (see, e.g., page 31, lines 24-28, emphasis added).

Nonetheless, solely to expedite prosecution of the application, Applicants have amended claim 26 to remove the recitation of "syngeneic." Such amendments are not made in acquiescence to the rejection, and Applicants reserve the right to prosecute claims of similar or differing scope.

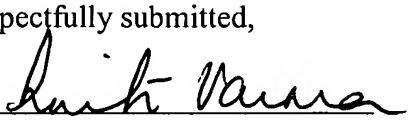
In light of the detailed description of the specification, one of skill in the art would readily appreciate that Applicants were in possession of the claimed invention at the time this application was filed. Accordingly, Applicants respectfully request reconsideration and withdrawal of all rejections for lack of written description.

CONCLUSION

For the foregoing reasons, Applicants respectfully request reconsideration and withdrawal of the pending rejections. Applicants believe that the claims are now in condition for allowance and early notification to this effect is earnestly solicited. Any questions arising from this submission may be directed to the undersigned at (617) 951-7000. If an additional fee is due, the Commissioner is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 18-1945, under Order No. VASG-P01-002. Please direct any questions arising from this submission to the undersigned at (617) 951-7000.

Dated: December 8, 2006

Respectfully submitted,

By 

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